SUPPORT FOR THE AMENDMENTS

Claim 1 is amended.

Claim 2 is canceled.

Support for the amendment of Claim 1 is provided by page 2, line 27 to page 3, line 2.

No new matter is added by the present amendment.

REMARKS

Claims 1 and 3-10 are pending in the present application.

In the Office Action, the Examiner has rejected Claims 1-6 and 9 as being obvious under 35 U.S.C. §103 over (a) Santus et al – US 5,296,236 and (b) Penkler et al (WO 97/18245) in view of Ream et al (US 2003/0003152). These grounds of rejection are respectfully traversed.

The examined claims require at least three components to be present:

(1) Tromethamine;

(2) An NSAID selected from ibuprofen, naproxen and flurbiprofen; and

(3) Glycine (and/or vitamin B6).

Santus disclose coating microgranules at column 6, lines 13-27 for the controlled release of an active ingredient. These microgranules are disclosed to contain buffers that include glycine. The examples each contain one of theophylline, ketorolac-trometamine (tromethamine), or naproxene. No specific example or even a specific disclosure is given of a composition that meets all three of the requirements above. The Examiner recognizes this deficiency in the disclosure of Santus, but cites to the disclosure at column 6, lines 13-27 and the exemplification of NSAIDs as active agents in the examples, including tromethamine and naproxene, and alleges that the claimed invention would be obvious.

Penkler is cited as disclosing compositions containing both tromethamine and an NSAID (i.e., naproxen) in Examples 1 and 3. The Examiner recognizes that Penkler fails to disclose the use of glycine; however, Ream is cited as disclosing tablets that contain glycine as a masking agent to improve organoleptic properties (see paragraph [0022] and [0063]).

Applicants disagree with the Examiner's allegations of obviousness for the following reasons.

The main result of the composition according to the present invention is to overcome the throat irritating effect of ibuprofen, naproxen and flurbiprofen. Santus discloses glycine as a buffer (column 6, lines 21-22). Penkler discloses that high levels of hydroxylamine (in particular, tromethamine) "gives a more palatable pharmaceutical formulation" (5th paragraph on page 12) and Ream discloses glycine "to assist in improving the organoleptic properties of the coating containing the medicament" (paragraph 0022), in particular, "in the case of a moderately bitter active ingredient, such as caffeine" (paragraph 0063).

However, none of the cited documents suggest how to avoid the throat-irritating effect of ibuprofen, naproxen and flurbiprofen. Thus, Applicants submit that the claimed invention would not be obvious. Further, to clearly differentiate from the cited art, the claims have been amended to specify the relative amount of tromethamine to the NSAIDs as being "from 0.2 to 2.5 parts by weight of tromethamine per one part by weight of NSAID". None of Santus, Penkler, or Ream disclose or suggest this specific relationship nor do they provide a reasonable expectation of the benefits flowing therefrom.

Applicants submit that even if a *prima facie* case of obviousness were present, "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)"

To this end, the Examiner's attention is directed to the Table on pages 8-9, which provide support and evidence of the unexpected effect according to the present invention. For ease of reference, the table is reproduced below:

Composition	Active Ingredient	Score
Solution A	Ibuprofen	21
Solution D	"	16
Solution G	"	11
Granulate L	"	8
Solution B	Flurbiprofen	15
Solution E	"	12
Solution H	"	9
Oral Spray M	"	6
Solution C	Naproxen	20
Solution F	"	17
Solution I	"	10
Granulate N	"	7

As stated above, the claimed invention is drawn to providing an oral dosage form for NSAIDs in which the throat-irritant stimulus is eliminated and which has good palatability. Although Ream shows that glycine can be used as a masking agent to improve organoleptic properties, there is nothing in any of Santus, Penkler, or Ream to suggest elimination of the throat-irritant stimulus.

In the Table on pages 8-9 (above), the following conclusions are made on page 9 of the specification:

> The evaluation of the compositions containing ibuprofen showed that Solution G (***corresponds to elected invention***) and the solution of Granulate L of the invention were less irritant and unpleasant and had a better palatability than the comparison Solutions A and D, not only for each individual sensation considered, but also for the sum of the evaluations obtained for all the sensations.

> The evaluation of the compositions containing flurbiprofen showed that Solution H (***corresponds to elected invention***) and the Oral Spray M of the invention were less irritant and unpleasant and had a better palatability than the comparison Solutions B and E, not only for each individual sensation considered, but also for the sum of the evaluations obtained for all the sensations.
>
> The evaluation of the compositions containing naproxen showed that Solution I (***corresponds to elected invention***) and the solution of Granulate N of the invention were less irritant and unpleasant and had a better palatability than the comparison Solutions C and F, not only for each individual sensation considered, but also for the sum of the evaluations obtained for all the sensations.

As evidenced by the foregoing, all the parameters in table on pages 8-9, i.e. burning, stinging, prickling and numbness, are referred to the throat-irritating effect of the pharmaceutical compositions comprising ibuprofen, naproxen or flurbiprofen.

Although such parameters are Subjective, they are well known in the art for the purpose asserted. For example, the same parameters were evaluated in the article cited on page 1, lines 20-22 of the present application to Breslin et. al., Chem. Senses 26: 55-65, 2001 (copy **submitted herewith**, see in particular, page 56, table 1).

Thus, the unexpected effect provided by the present invention is to overcome the "chemesthetic effect" (irritant effect) on the oral cavity, throat and pharynx, which is a typical side effect of "a number of" NSA1D but not of "all" NSAIDs, as stated on page 1, lines 18-20 of the present application.

This is also confirmed in EP 1 974 751 (copy **submitted herewith**, see paragraph (0002]), according to which *"NSAIDs from the group of naphthalene or benzene acetic acid derivatives* (...) *have* a *chemesthetic (irritant effect) on the oral cavity, throat and pharynx."*

Thus, the skilled artisan would know that ketorolac does not belong to the above-classes of derivatives. As such, the substitution of ketorolac with ibuprofen in the composition of Santus would have lead to an oral pharmaceutical composition having the

throat-irritating chemesthetic effect of ibuprofen and, thus, unsatisfactory for the intended purpose of Santus. The Examiner is reminded that "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)

For the foregoing reasons, contrary to the Examiner's allegations, the skilled artisan would not use *any* NSAID in combination with tromethamine, nor would the artisan had a reasonable expectation of success in so doing.

In view of the foregoing, withdrawal of these grounds of rejection is requested.

Upon the allowability of the elected claims, the Examiner is reminded of the right to rejoinder in MPEP 821.04. An action tot his effect is requested.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, L.L.P.
Richard. L .Treanor, Ph.D.

Vincent K. Shier, Ph.D.
Registration No. 50,552

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)